or more coding groups from the coding sequence, and thereafter correlating mass spectral peaks of the mass spectral fragment ions with the molecular ion of the fragment Y^a to identify the sequence of the individual coding groups.

36. (Amended) A method of A method of identifying a pharmaceutically useful substrate comprising preparing a library containing a plurality of chemical constructs as defined in claim 1, and subjecting the library to biological testing to identify biologically active substrates.

REMARKS

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Applicants have attached an abstract on a separate sheet of paper as required by US practice. Applicants have amended the specification for purposes of adding the priority information. The claims have been amended to place them in form appropriate to US practice.

Respectfully Submitted,

Date: 4/5/2001

Frank P. Grassler
Registration No. 31,164

GlaxoSmithKline
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709
Phone: 919-483-2482
Fax: 919-483-7988

Version with markings to show changes made

6. (Amended) A chemical construct according to [any one of the preceding claims] claim 1 wherein each solid support contains a coding tag or coding sequence which encodes information indicative of at least part of the synthesis history of the construct.

12. (Amended) A chemical construct according to [any one of the preceding claims] claim 1 wherein a proportion of the total substrate R in the construct is linked to the solid support by means of a connecting group Y^b having a cleavage site which is cleavable to release a fragment F^b from the solid support, the fragment F^b comprising the substrate R and at least a portion of the connecting group Y^b; the connecting group Y^b not being cleavable to release substrate R under conditions effective to cleave the second cleavage sites in the groups Y^1R and Y^2R and wherein:
(i) the chemical fragment F^b contains a sensitising group G which sensitises the chemical fragment F^b to instrumental, e.g. mass spectroscopic analysis and/or:
(ii) the fragment F^b contains a means for imparting a characteristic signature to the mass spectrum of the fragment.

13. (Amended) A chemical construct according to [any one of the preceding claims] claim 1 wherein the sensitising group G is generated by cleavage at the first cleavage site of the group Y^1 or Y^2 or, when present, Y^a or the said cleavage site of Y^b.

14. (Amended) A chemical construct according to [any one of the preceding claims] claim 1 wherein the sensitising group G is a basic amino group or a carboxylate group, preferably a basic amino group.

17. (Amended) A construct according to [any one of the preceding claims] claim 1 wherein the fragment Fr and (where present) optionally the fragment F^a and (where present) optionally the fragment F^a contain a means for imparting a characteristic signature to the mass spectrum of the fragment.

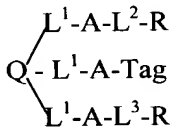
20. (Amended) A chemical construct according to claim 18 [or claim 19] wherein the isotopic label comprises an atom or atoms selected from $^1H/H^2$ (D), $^{79}Br/^{81}Br$, $^{12}C/^{13}C$, $^{14}N/^{15}N$ and $^{16}O/^{18}O$.

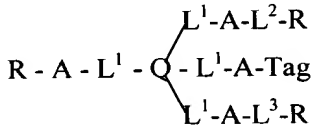
21. (Amended) A chemical construct according to [any one of claims 18 to 20] claim 18 wherein the isotopic label(s) is/are located between the first and second cleavage sites of the groups Y^1 and Y^2.

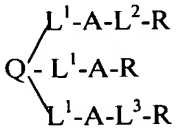
22. (Amended) A chemical construct as defined in [any one of the preceding claims] claim 1 wherein the first and second cleavage sites in the groups Y^1 are defined by first and second linker groups L^1 and L^2, first and second cleavage sites in the group Y^2 are defined by first and second linker groups L^1 and L^3, the cleavage site in the group Y^a (where present) is defined by a linker group L^a and the cleavage site in the group Y^b (where present) is defined by a linker group L^b.

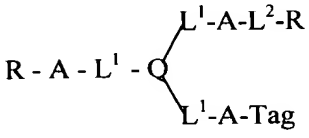
24. (Amended) A chemical construct according to claim 22 [or claim 23] wherein a spacer group A is interposed between each pair of first and second linker groups, or between the linker group L^a and the coding tag, or between the linker group L^b and the substrate R, the spacer group A containing an isotopic peak splitting label.

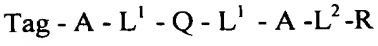
25. (Amended)A chemical construct according to [any one of the preceding claims] claim 1 having a formula selected from the group consisting of:

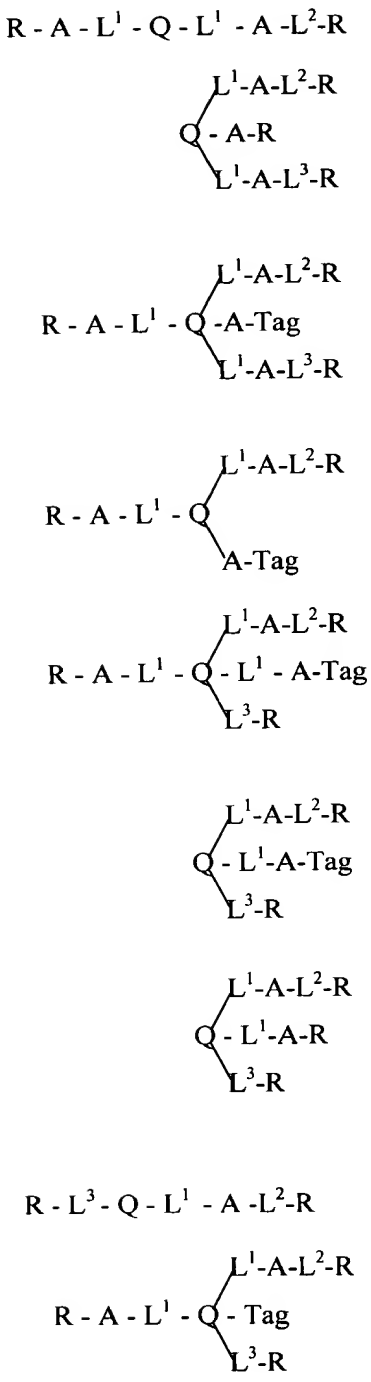












wherein L^1, L^2, L^3, A and R are as defined in [any one of the preceding claims] claim 1 and "Tag" represents a coding sequence.

26. (Amended) A construct as claimed in [any one of claims 1 to 25] claim 1 for use in a tiered release method of screening, the construct having the formula Tag - A - L^1 - Q - L^1 - A -L^2

- R wherein Tag, A, L^1 , Q ,L^2 and R are as defined [in any one of the preceding claims] claim 1.

27. (Amended) A chemical construct according to [any one of the preceding claims] claim 1 wherein the orthogonally cleavable cleavage sites can be cleaved by a reactions selected from acid catalysed cleavage, base catalysed cleavage, oxidative cleavage, reductive cleavage, nucleophilic displacement, electrophilic displacement, and thermal, photochemical and enzymatic cleavage.

28. (Amended) Intermediate chemical constructs for use preparing a chemical construct as defined in [any one of the preceding claims] claim 1, the intermediate constructs having the formulae $Y^{1'}$-Q-$Y^{2'}$, RY^1-Q-$Y^{2'}$and $Y^{1'}$-Q-Y^2R wherein $Y^{1'}$ and $Y^{2'}$ are reactive or protected forms of the group Y; and R, Q and Y are as defined in [any one of the preceding claims] claim 1.

29. (Amended) Intermediate constructs of the formulae $L^{2'}$-A-L^1-Q-L^1-A^p, R-L^2-A-L^1-Q-L^1-A^p, $L^{3'}$-A-L^1-Q-L^1-A^p, R-L^3-A-L^1-Q-L^1-A^p, R-L^3-A-L^1-Q-L^1-A-$L^{2'}$ and $L^{3'}$-A-L^1-Q-L^1-A-L^2-R wherein $L^{1'}$, $L^{2'}$ and $L^{3'}$ are reactive or protected forms of the linker groups L^1, L^2 and L^3, A^p is a reactive or protected form of the spacer group A containing a peak splitting isotopic label, and Q, R, A, L^1, L^2 and L^3 are as defined in [any one of the preceding claims] claim 1.

31. (Amended) An intermediate construct according to claim 29 [or claim 30] wherein the solid support has bonded thereto a coding tag sequence L^1-A-Tag and/or a sequence R - A - L^1 -, or a precursor form thereof.

32. (Amended) A differential release method of assaying a chemical library for biological activity, the method comprising:

(i) subjecting a construct comprising a solid support Q having linked thereto groups Y^1R and Y^2R as defined in [any one of the preceding claims] in claim 1 to cleavage conditions effective to release substrate R from the group Y^1R;

(ii) testing the substrate R released from the group Y^1R in a biological assay;

(iii) subsequently subjecting the construct to cleavage conditions effective to release substrate R from the group Y^2R; and

(iv)) testing the substrate R released from the group Y^2R in a biological assay.

33. (Amended) A tiered release method of assaying a chemical library for biological activity, the method comprising:

(i) subjecting a construct as claimed in [any one of] claim[s] 1 [to 27] to cleavage conditions effective to release a first portion of the substrate R from the group Y^1R;

(ii) testing the first portion of substrate R released from the group Y^1R in a biological assay;

(iii) subjecting the construct to cleavage conditions effective to release a second portion of the substrate R from the group Y^1R; and

(iv) testing the second portion of substrate R released from the group Y^1R in a biological assay.

34. (Amended) A method of determining the identity of a substrate R linked to a solid support Q of a construct as claimed in [any one of] claim[s] 8 [to 27] by mass spectrometric means; the solid support Q having a coding sequence attached thereto by means of a connecting group Y^a having a cleavage site cleavable to release a fragment F^a from the solid support, the fragment F^a comprising the coding sequence and at least a portion of the connecting group Y^a, wherein (i) the chemical fragment F^a contains a sensitising group G which sensitises the chemical fragment F^a to mass spectroscopic analysis;

the coding sequence comprising a sequence of coding groups the nature and order of which is indicative of the identity of the substrate R;

the method comprising cleaving the connecting group Y^a so as to release the fragment F^a from the solid support; subjecting the fragment Y^a to mass spectrometry under conditions effective to bring about mass spectral fragmentation of the coding group and the formation of mass spectral fragment ions corresponding to the loss of one or more coding groups from the coding sequence, and thereafter correlating mass spectral peaks of the mass spectral fragment ions with the molecular ion of the fragment Y^a to identify the sequence of the individual coding groups.

36. (Amended) A method of A method of identifying a pharmaceutically useful substrate comprising preparing a library containing a plurality of chemical constructs as defined in [any of the preceding claims] claim 1, and subjecting the library to biological testing to identify biologically active substrates.